A DISSERTATION

ON

SERUM URIC ACID LEVEL IN TYPE 2 DIABETES MELLITUS

Submitted to
THE TAMILNADU DR. M. G. R. MEDICAL UNIVERSITY
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M.D DEGREE IN GENERAL MEDICINE
BRANCH I

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CERTIFICATE

This is to certify that the dissertation entitled **"A Study on Serum Uric Acid Level in Type 2 Diabetes Mellitus"** is a bonafide work done by **Dr. P.SENTHILNATHAN** in **M.D BRANCH I GENERAL MEDICINE** at Government Mohan Kumaramangalam Medical College, Salem-636030, to be submitted to The Tamil Nadu Dr.M.G.R Medical University, in fulfilment of the University Rules and Regulation for the award of M.D. Degree Branch I General Medicine, under my supervision and guidance, during the academic period from March 2009 to October 2009.

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DECLARATION

I solemnly declare that this dissertation **"A Study on Serum Uric Acid Level in Type 2 Diabetes Mellitus"** was prepared by me at Government Mohan Kumaramangalam Medical College and Hospital, Salem-636030 under the guidance and supervision of **Prof.Dr.T.SUNDARARAJAN, M.D.,** Professor of General Medicine, Govt. Mohan Kumaramangalam Medical College and Hospital Salem.

This dissertation is submitted to The Tamil Nadu Dr. M.G.R. Medical University, Chennai in fulfillment of the University regulations for the award of the degree of M.D. Branch I General Medicine.

Place : Salem

Date :

(Dr. P.SENTHILNATHAN)

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CONTENTS

ABBREVIATIONS

IDDM	- Insulin Dependent Diabetes Mellitus
NIDDM	- Non Insulin Dependent Diabetes Mellitus
CAD	- Coronary Artery Disease
JNC	- Joint National Committee
IHD	- Ischaemic Heart Disease
GDM	- Gestational Diabetes Mellitus
SUA	- Serum Uric Acid
HT	- Hypertension
BMI	- Body Mass Index
WHR	- Waist Hip Ratio
DOD	- Duration of Diabetes
BS	- Blood Sugar
PG	- Plasma Glucose
MI	- Myocardial Infarction
I	- Ischaemia
SD	- Standard Deviation
IFG	- Impaired Fasting Glucose
IGT	- Impaired Glucose Tolerance
CVD	- Cardiovascular Disease
IDF	- International Diabetic Federation

INTRODUCTION

Cardiovascular disease has emerged as a major health burden worldwide.[1] Type 2 diabetes mellitus is an epidemic in India for the past few decades. Diabetes mellitus is the most important risk factor associated with two to four fold increased incidence of coronary artery disease.[2]

Nearly 120 years have elapsed since serum uric acid was first described as risk factor for cardiovascular disease.[3] Serum uric acid as a potential cardiovascular disease risk factor has ballooned in the last several years with numerous abstracts & research papers, multiple editorials & review articles.

The four major risk factors for CAD viz, hypercholesterolemia, hypertension, diabetes mellitus, and cigarette smoking which were present in Framingham's cohort are difficult to explain among Indians with CAD. CAD in Indians is present even with low cholesterol level.[4] Obesity, systemic hypertension, hypercholesterolemia is associated with Type 2 DM, as a result of insulin resistance state.[5]

Much but not all epidemiological research identifies hyperuricemia as a independent risk factor for the development of cardiovascular disease, renal disease & stroke, particularly in patients with hypertension or congestive heart failure and in women.[6]

Hyperuricemia has been found to be associated with obesity and insulin resistance, and consequently with type 2 diabetes.[7] Further potentially important biological effects of uric acid relate to endothelial dysfunction by inducing antiproliferative effects on endothelium and impairing nitric oxide production and inflammation.[8,9] Uric acid may play a role in immune activation with subsequent increased chemokine and cytokine expression.[10,11]

Puig et al has found that in patients with metabolic syndrome serum uric acid level was higher when compared with controls and that serum urate increases with the number of components of metabolic syndrome.[12] In addition a recent study in rats showed that fructose – induced hyperuricemia plays a pathogenic role in the metabolic syndrome.[13]

Some have found a significant & specific independent association between uric acid level and cardiovascular mortality and morbidity, while others have come to an opposite conclusion.[14] Thus despite abundant epidemiological evidence, the role of increased serum uric acid and cardiovascular risk is controversial.

Here an attempt has been made to study the level of serum uric acid level in Type 2 diabetes mellitus & the correlation between elevated serum uric acid level and the component of metabolic syndrome like obesity, hypertension, dyslipidemia.

AIMS AND OBJECTIVES

1) To identify the level of uric acid in patients with type 2 Diabetes mellitus.

2) To identify whether any association exist between age, sex, anthropometric measurements (BM1, WHR), hypertension, dyslipidemia & coronary artery disease with serum uric acid level.

REVIEW OF LITERATURE

DIABETES MELLITUS

Diabetic Mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in Insulin secretion, insulin action or both.[15] The chronic hyperglycemia of diabetes is associated with long term damage, dysfunction and failure of various organs, especially the eyes, kidneys, nerves, heart and blood vessels.[16]

CLASSIFICATIONS:

In 1997, ADA issued new diagnostic and classification criteria; In 2003, modifications were made regarding the diagnosis of impaired fasting glucose.[17] The classification of diabetes includes four clinical classes,

- Type 1 Diabetes: Results from β-cell destruction, usually leading to absolute insulin deficiency.
- Type 2 Diabetes: Results from a progressive insulin secretory defect on the background of insulin resistance.
- Other specific types of diabetes due to other causes, eg.(i) genetic defects in β-cell functions, (ii) Diseases of exocrine

pancreas, (such as cystic fibrosis), (iii) Drug or chemical induced (such as in treatment of AIDS or after organ transplantation)

- ☛ Gestational Diabetes Mellitus (GDM): Diabetes diagnosed during pregnancy.

DIAGNOSIS OF DIABETES:

RECOMMENDATIONS:

1. The Fasting Plasma Glucose (FPG) test is the preferred test to diagnose diabetes in children and non pregnant adults.
2. Use of the A_1C for the diagnosis of diabetes is not recommended at this time.[18]

Three ways to diagnose diabetes are available and each must be confirmed on a subsequent day unless equivocal symptoms of hyperglycemia are present. Although the 75 g. oral glucose tolerance test (OGTT) is more sensitive and modestly more specific than the FPG to diagnose diabetes, it is poorly reproducible and difficult to perform in practice. Because of ease of use, acceptability to patients, and lower cost, the FPG is the preferred diagnostic test.[19]

CRITERIA FOR THE DIAGNOSIS OF DIABETES

1. FPG ≥126 mg/dl (7.0 mmol/l). Fasting is defined as no caloric intake for atleast 8 hours. (or)
2. Symptoms of Hyperglycemia and a casual plasma glucose ≥ 200 mg/dl (11.1 mmol/l). Casual is defined as any time of day without regard to time since last meal. The classic symptoms of Hyperglycemia include polyuria, polydipsia and unexplained weight loss. (or)
3. 2 hours plasma glucose ≥ 200 mg/dl (11.1 mmol/l) during an OGTT. The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose load containing the equivalent of 75g. anhydrous glucose dissolved in water.[17]

DIAGNOSIS OF PRE-DIABETES

Hyperglycemia not sufficient to meet the diagnostic criteria for diabetes is categorized as either Impaired Fasting Glucose or Impaired Glucose tolerance, depending on whether it is identified through the FPG or the OGTT.

IFG = FPG 100 mg/dl – 125 mg/dl

IGT = 2 hr. plasma glucose 140 mg/dl – 199 mg/dl.

IFG and IGT has been officially termed "Pre-diabetes". Both IGT and IFG are similarly associated with endovascular disease outcomes. Risks are higher when IGF and IFG coexist. Lifestyle interventions are highly effective in delaying or preventing the onset of diabetes in people with IGT and may reduce LVD and total mortality.[20]

EPIDEMIOLOGY

The prevalence of diabetes is rapidly rising all over the globe at an alarming rate.[21] Although there is an increase in the prevalence of type 1 diabetes also, the major driver of the epidemic is the type 2 DM, which accounts for more than 90%.

India leads the world with largest number of diabetic subjects earning the dubious distinction of being termed the "**diabetes capital of the world"**.[22] According to the Diabetes Atlas 2006 published by

the IDF, the number of people with diabetes in India currently around 40.9 million is expected to rise to 69.9 million by 2025.[23,24](Fig.1).

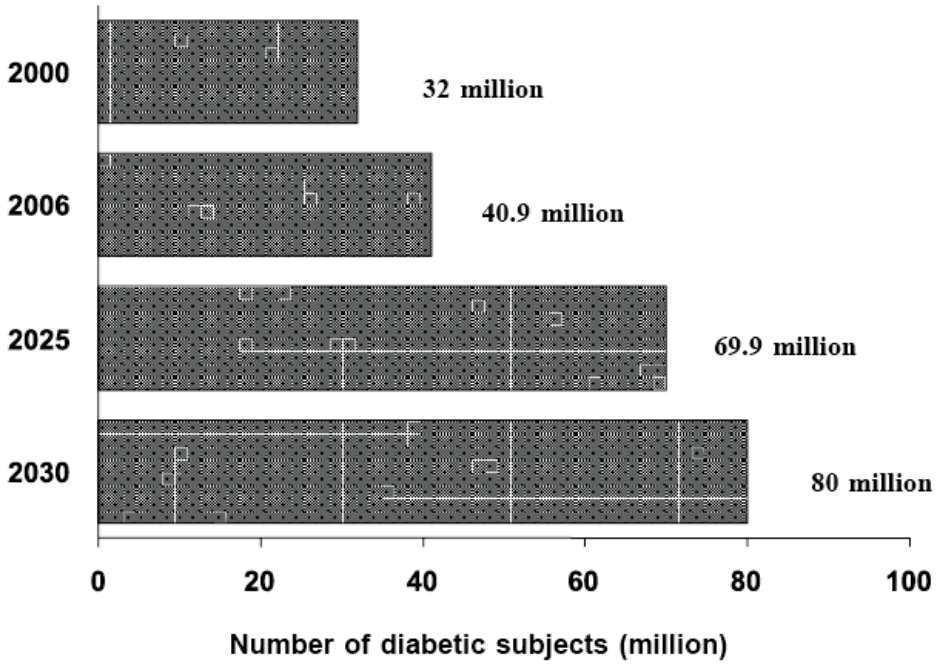


Fig. 1. Estimated number of diabetic subjects in India.

Fig.2 is a map of India showing the prevalence of type 2 DM reported in different regions of India.

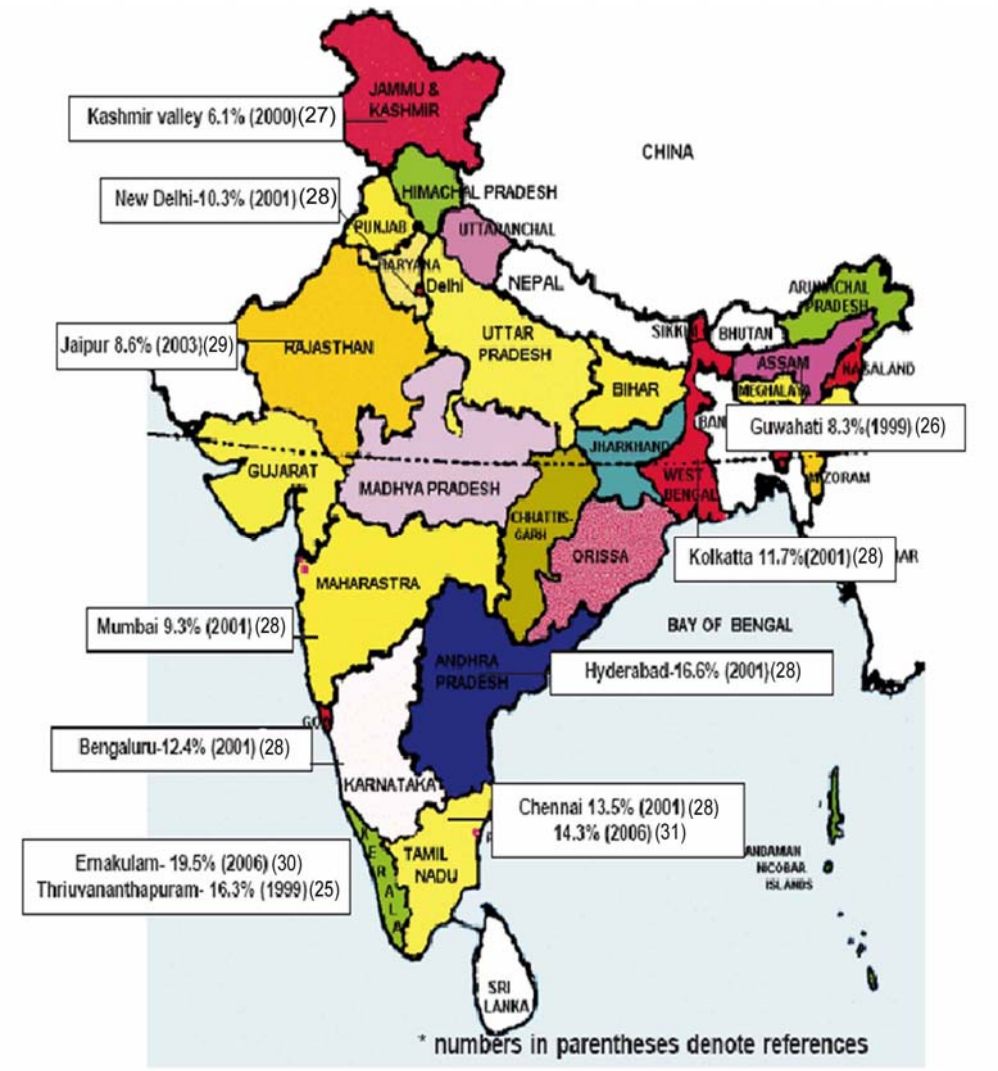


Fig. 2. Recent population based studies showings the prevalence of type 2 diabetes in different parts of India.

A study conducted by WHO & ICMR in 5 states of India, representing each zone has shown that the highest prevalence of DM was in urban areas followed by peri-urban and rural areas.[32]

The increase in the prevalence of type 2 DM among Indians is attributed to both genetic and environmental factors. The so called "Asian Indian Phenotype" refers to certain unique clinical and biochemical abnormalities in Indians which include increased insulin resistance, greater abdominal obesity, lower adiponectin and higher high sensitive C-reactive protein levels.[33,34,35] This phenotype makes Asian Indians more prone to diabetes and premature coronary artery disease.

However, the primary driver of the epidemic of diabetes is the rapid epidemiological transition associated with changes in dietary patterns (Fast food culture)[36] and decreased physical activity (Sedentarinism),[37] as evident from the higher prevalence of diabetes in the urban population.[38]

Even though the prevalence of microvascular complication of diabetes like retinopathy and nephropathy are comparatively lower in

Indians, the prevalence of premature coronary artery disease is much higher in Indians compared to other ethnic groups.[38]

The most disturbing trend is the shift in age of onset of diabetes to a younger age in recent years. Mohan et al has recently developed the Indian Diabetes Risk Score (IDRS) using four simple variables namely, age, family history, regular exercise and waist circumference (Table).[39]

Table. Indian Diabetes Risk Score (IDRS)

Particulars	Score
***Age (yr)*:**	
< 35 (reference)	0
35-49	20
>50	30
***Abdominal obesity*:**	
Waist <80 cm (female), <90 (male) (reference)	0
Waist > 80-89 cm (female), >90-99 cm (male)	10
Waist >90 cm (female), >100 cm (male)	20

***Physical activity*:**

Vigorous exercise or strenuous (manual) labour at home/work	0
Mild to moderate exercise or mild to moderate physical activity at home/work	20
No exercise and sedentary activities at home/work	30

***Family history*:**

No family history (reference)	0
Either parent	10
Both parents	20
Minimum score	0
Maximum score	100

Interpretation:

Score < 30 low risk, score 30-50 medium risk and score > 60 high risk for type 2 diabetes and cardiovascular diseases.

PATHOGENESIS:

Insulin resistance and abnormal insulin secretion are central to the development of type 2 DM. Although the primary defect is controversial, most studies support the view that insulin resistance

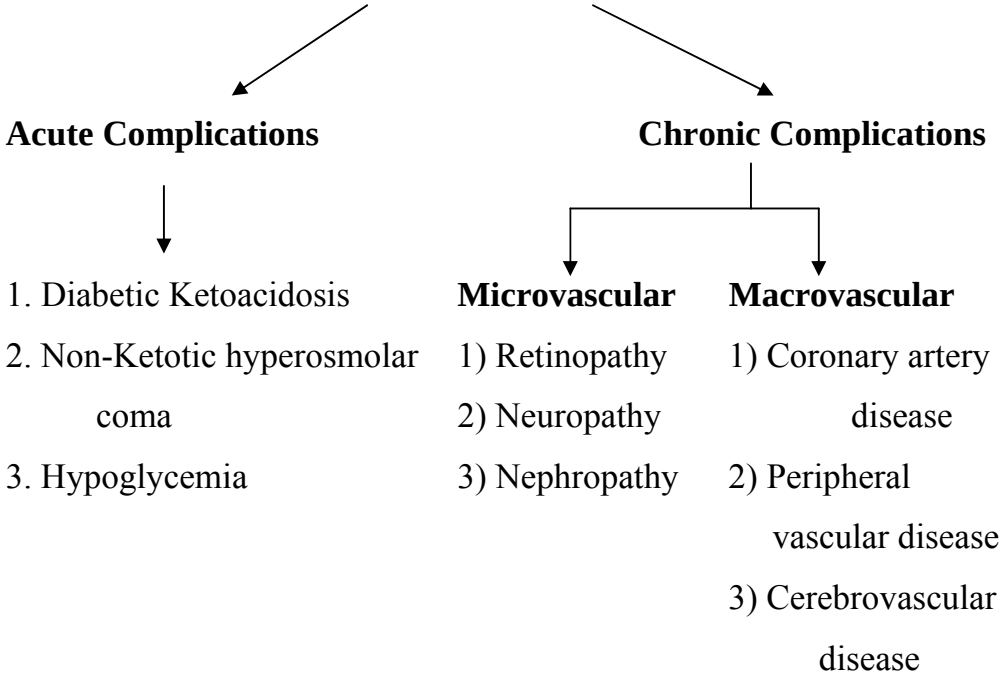
precedes an insulin secretory defect but that diabetes develops only when insulin secretion becomes inadequate.[40]

Type 2 DM has a strong genetic component. The concordance of Type 2 DM in identical twins is between 70 and 90%. Individuals with a parent with type 2 DM have an increased risk of diabetes; if both parents have type 2 DM, the risk approaches 40%. A recent study has found a strong association of type 2 diabetes mellitus with a variant of the transcription factor 7- like 2 gene in several populations.[40]

The disease is polygenic and multifactorial since in addition to genetic susceptibility, environmental factors (such as obesity, nutrition and physical activity) modulate the phenotype.

In the early stages of the disorder, glucose tolerance remains near normal, despite insulin resistance, because the pancreatic beta cells compensate by increasing insulin output. As the disorder progresses, the beta cells are unable to sustain the hyperinsulinemic state. IGT, characterized by elevations in postprandial glucose, then develops. A further decline in insulin secretion and an increase in hepatic glucose production lead to overt diabetes with fasting hyperglycemia. Ultimately, beta cell failure may ensue.[40]

COMPLICATIONS OF DIABETES MELLITUS[40]



Others

1. Gastrointestinal – Gastroparesis, diarrhea.
2. Genitourinary – Uropathy / Sexual dysfunction
3. Dermatological – Acanthosis nigricans.
4. Infections – Emphysematous pyelonephritis, Mucormycosis, Candidiasis.

METABOLIC SYNDROME

Metabolic syndrome is a combination of medical disorders that increase the risk of developing cardiovascular disease and diabetes.

Metabolic syndrome is also known as syndrome X, insulin resistance syndrome, Reaven's syndrome, and CHAOS (Australia).[41]

HISTORY

The term "metabolic syndrome" dates back to at least the late 1950s,

The Marseilles physician Dr. Jean Vague, in 1947, observed that upper body obesity appeared to predispose to diabetes, atherosclerosis, gout and calculi.[42]

In 1977, Haller used the term "**metabolic syndrome**" for associations of obesity, diabetes mellitus, hyperlipoproteinemia, **hyperuricemia**, and Hepatic steatosis when describing the additive effects of risk factors on atherosclerosis.[43]

The same year, Singer used the term for associations of obesity, gout, diabetes mellitus, and hypertension with hyperlipoprotenemia.[44]

In 1988, in his Banting lecture, Gerald M. Reaven proposed insulin resistance as the underlying factor and named the constellation of abnormalities Syndrome X. Reaven did not include abdominal obesity, which has also been hypothesized as the underlying factor, as part of the condition.[45]

RISK FACTORS [40]

- Overweight / Obesity
- Sedentary Lifestyle
- Stress
- Aging
- Diabetes Mellitus
- Coronary Heart Disease
- Lipodystrophy

ETIOLOGY

INSULIN RESISTANCE

The most accepted and unifying hypothesis to describe the pathophysiology of the metabolic syndrome is insulin resistance, caused by an incompletely understood defect in insulin action. The onset of insulin resistance is heralded by postprandial

hyperinsulinemia, followed by fasting hyperinsulinemia and, ultimately, hyperglycemia.

An early major contributor to the development of insulin resistance is an overabundance of circulating fatty acids. The inhibition of lipolysis in adipose tissue is the most sensitive pathway of insulin action. Thus, when insulin resistance develops, increased lipolysis produces more fatty acids, which further decrease the antilipolytic effect of insulin. Excessive fatty acids enhance substrate availability and create insulin resistance by modifying downstream signaling. Fatty acids impair insulin-mediated glucose uptake and accumulate as triglycerides in both skeletal and cardiac muscle, whereas increased glucose production and triglyceride accumulation are seen in liver.[40]

Increased Waist Circumference

Relative increases in visceral versus subcutaneous adipose tissue with increasing waist circumference in Asian Indians explains the greater prevalence of the syndrome in these populations. It is also possible that visceral fat is a marker for, but not the source of, excess postprandial FFAs in obesity.[40]

Dyslipidemia

The major lipoprotein disturbances are hypertriglyceridemia & decrease in HDL.

Hypertriglyceridemia is an excellent marker of the insulin-resistant condition.

With fasting serum triglycerides >2.0 mM (~180 mg/dL), there is almost always a predominance of small dense LDLs. Small dense LDLs are thought to be more atherogenic.[40]

Glucose Intolerance

The defects in insulin action lead to impaired suppression of glucose production by the liver and kidney and reduced glucose uptake and metabolism in insulin-sensitive tissues, i.e., muscle and adipose tissue.[40]

Hypertension

In the setting of insulin resistance, the vasodilatory effect of insulin is lost, but the renal effect on sodium reabsorption and increase in the activity of the sympathetic nervous system is preserved, which leads to hypertension.[40]

Proinflammatory Cytokines

The increases in proinflammatory cytokines, including interleukin (IL) 1, IL-6, IL-18, resistin, tumor necrosis factor (TNF) , and C-reactive protein (CRP), reflect overproduction by the expanded adipose tissue mass. Adipose tissue-derived macrophages may be the primary source of pro-inflammatory cytokines locally and in the systemic circulation.[40]

Adiponectin

Adiponectin is an anti-inflammatory cytokine produced exclusively by adipocytes. Adiponectin enhances insulin sensitivity and inhibits many steps in the inflammatory process. In the liver, adiponectin inhibits the expression of gluconeogenic enzymes and the rate of glucose production. In muscle, adiponectin increases glucose transport and enhances fatty acid oxidation, partially due to activation of AMP kinase. Adiponectin is reduced in the metabolic syndrome.[46,47]

In addition to the features specifically associated with metabolic syndrome, insulin resistance is accompanied by other metabolic alterations. These include increases in,

- **Uric acid**[48]
- apoB and C III,
- prothrombotic factors (fibrinogen, plasminogen activator inhibitor 1),
- serum viscosity,
- asymmetric dimethylarginine,
- homocysteine,
- white blood cell count,
- CRP,
- microalbuminuria,
- nonalcoholic fatty liver disease (NAFLD) and/or nonalcoholic steatohepatitis (NASH)
- polycystic ovarian disease (PCOS), and
- obstructive sleep apnea (OSA).[40]

Diagnosis

There are currently two major definitions for metabolic syndrome provided by the International Diabetes Federation and the revised National Cholesterol Education Program, respectively.

IDF

The IDF consensus worldwide definition of the metabolic syndrome.[49]

Central obesity (defined as waist circumference with ethnicity specific values), ≥ 90 cm in men and ≥ 80 cm in women for South Asian and Chinese people.

AND any two of the following:

Raised triglycerides : > 150 mg/dL (1.7 mmol/L), or specific treatment for this lipid abnormality.

Reduced HDL cholesterol: < 40 mg/dL (1.03 mmol/L) in males, < 50 mg/dL (1.29 mmol/L) in females, or specific treatment for this lipid abnormality.

Raised blood pressure : systolic BP > 130 or diastolic BP >85 mm Hg, or treatment of previously diagnosed hypertension.

Raised fasting plasma glucose :(FPG)>100 mg/dL (5.6 mmol/L), or previously diagnosed type 2 diabetes.

If BMI is >30 kg/m², central obesity can be assumed and waist circumference does not need to be measured.

NCEP

The US National Cholesterol Education Program Adult Treatment Panel III[50] requires at least three of the following:

Central obesity: waist circumference ≥ 102 cm or 40 inches (male), ≥ 88 cm or 36 inches(female)

Dyslipidaemia: TG ≥ 1.695 mmol/L (150 mg/dl)

Dyslipidaemia: HDL-C < 40 mg/dL (male), < 50 mg/dL (female) blood pressure ≥ 130/85 mmHg

Fasting plasma glucose ≥ 6.1 mmol/L (110 mg/dl).

The two differences are that IDF state if BMI>30 kg/m^2 central obesity can be assumed and waist circumference does not need to be measured. However, this potentially excludes any subject without increased waist circumference if BMI<30, whereas, in the NCEP definition, metabolic syndrome can be diagnosed based on other criteria and the IDF uses geography-specific cut points for waist circumference, while NCEP uses only one set of cut points for waist circumference regardless of geography. These two definitions are much closer to each other than the original NCEP and WHO definitions.

CAUSES OF HYPERURICEMIA IN TYPE 2 DIABETES MELLITUS PATIENTS

1. DIETARY HABITS

An increase in Serum urate level may occur in type 2 DM in various situations like Purine rich diet such as liver, anchovies, kidney, sardines, sweet breads, peas, cauliflower, brinjal and yeasts.[40]

2. ALCOHOL

Alcohol increases serum urate level by accumulation of organic acids (betahydroxybutyrate, acetoacetate, lactate) that compete with urate for tubular secretion and accelerated breakdown of ATP by liver is increased (Beer contains high uric acid).[40]

3. OBESITY

Various mechanisms play role in increase in serum urate by obesity, like anabolic effects of tissues because of Insulin resistance, increase in denovo biosynthesis of Purines, decreased excretion and increased breakdown.[40]

4. DEHYDRATION

Dehydration can impair uric acid excretion by decreased filtration and secretion and sometimes with acidosis by competition of H^+ ion for excretion. Starvation again causes accumulation of organic acids that compete for the excretion of urate for tubular secretion.[40]

5. SYSTEMIC HYPERTENSION

There are various studies regarding association of systemic hypertension with the elevated uric acid level. Probable mechanism suggested is impaired excretion of urate because of intrinsic renal defect in hypertension.[40]

6. LACTIC ACIDOSIS AND DIABETIC KETOACIDOSIS

Dehydration and Pre renal azotemia both can impair filtration and secretion of urate leading to retention and also these may cause diminished reabsorption of uric acid. Again in the setting of acidosis H^+ ion compete with uric acid leading to enhanced reabsorption and retention.[40]

7. HYPERGLYCEMIA

Both uric acid and glucose levels are positively related to body mass index. The association of uric acid in relation to glucose reflects the biochemical interaction between serum glucose metabolism and purine metabolism.[40]

8. RENAL INSUFFICIENCY

Decreased urate filtration contributes to the hyperuricemia of renal insufficiency. But the correlation between BUN, Serum creatinine and serum uric acid concentration per unit of GFR increases progressively with renal insufficiency. The tubular secretory capacity tends to be preserved, the tubular reabsorbtive capacity is decreased and extra renal clearance of uric acid increases as the renal damage becomes more severe.[40]

9. DRUGS

They mainly act by competitive inhibition of uric acid excretion. Salicylates and nicotinic acid directly compete with the urate for tubular secretion. Diuretics, L-dopa, Pyrazinamide, Ethambutol, cyclosporine decreases the secretion of urate in the tubules.[40]

URIC ACID AND INSULIN RESISTANCE

Nearly 120 years have elapsed since uric acid was first described as a potential factor in the development of cardiovascular disease.[3] The actual mechanism of hyperuricemia found in many diabetic patients is not known, but different theories have been presented.

Quinones et al observed that hyperuricemia is a frequent finding in Insulin resistant states. He found that insulin induces changes in fractional uric acid and sodium excretion co-related with one another and physiological hyperinsulinemia acutely reduces urinary uric acid and sodium excretion in coupled patients. They also observed that in Insulin resistant individuals compensatory hyperinsulinemia imposes a chronic antinatriuretic and anti uricosuric pressure on the kidney.[51]

Moriwaki et al studied the effects of glucose infusion on the renal clearance of uric acid, xanthine and oxypurinol and found that the effect was not related to osmotic diuresis, but induced by glycosuria and hyperglycemia.[52]

Muscilli et al observed that effect of insulin or urinary excretion in normal subjects and found that hyperinsulinemia caused a significant decrease in the urinary excretion of uric acid.[53]

Tkac et al found that higher mean serum uric acid level in myocardial infarction group was associated with increasing age and serum creatinine levels. It was associated with elevated TGL, BMI and hypertension.[54]

Woo et al study results found positive association between serum uric acid concentration and BMI, with systolic and diastolic BP, urea, creatinine, fasting glucose 2 hour insulin, TGL, apolipoprotein B in men. Similar but fewer associations were seen in women with additional positive associations with age. The study suggests that serum uric acid may be a Marker for the presence of an adverse cardiovascular risk profile.[55]

Wannamethee et al conducted in their study that serum uric acid is not a truly independent risk factor for coronary acting disease. Increased serum uric acid appears to be an integral part of the cluster of risk factors associated with the insulin resistance syndrome that

include central obesity, increased TG level and serum cholesterol level.[56]

Pearl et al study concluded high molar equivalent serum anti oxidant capacity (MESA) between diabetics and non-diabetics showed uric acid as a free radical scavenger is NIDDM.[57]

There are certain clinical clustering groups with increased cardiovascular risk, which have associated hyperuricemia.[58] They are,

1. African American patient group.
2. Patients group with excessive alcohol consumption.
3. Hypertensive patient groups
4. Non diabetic patient groups with acclerated atherosclerosis.
5. Congestive heart failure patients group with ischemic cardiomyopathy.
6. Metabolic syndrome patients group
7. Renal disease patients group and
8. Patients group taking diuretics.

Each of the clustering group has metabolic mechanism that may help to explain why serum uric acid may be elevated.

MECHANISM:

Type 2 Diabetics mellitus is strongly associated with hyperuricemia.[59]

Potential mechanism involved in the association of hyperuricemia and type 2 Diabetes mellitus include the following:

1. Altered renal sodium handling causes decreases renal blood flow and diminishes uric acid excretion.[60]
2. Decreased GFR stimulating urate absorption.[61]
3. Microvascular disease resulting in local tissue ischemia.
4. Ischemia associated with increased lactate production.
5. Ischemia induces increased xanthine oxidase production.[61]

Other factors which may contribute are alcohol abuse, lead intake, obesity, insulin resistance and diuretic use.

Mechanism of Hyperuricemia in Hyperinsulinemia[61]

Hyperinsulinemia

↓

Altered renal sodium handling

↓

↑Arterial pressure

↓Renal blood flow

↓Uric acid excretion

↓

Hyperuricemia

Increased serum uric acid has been found to predict the development of renal insufficiency in individuals with normal function.

In type 2 Diabetes mellitus hyperuricemia seems to be associated with metabolic syndrome and with early onset or increased progression to overt nephropathy.

From the review the following conclusion was arrived:

Determining the truth in medical science is a difficult business. Serum uric acid may or may not be an independent risk factor because its linkage to other risk factors is so strong. However there is not much correlation regarding its role as a marker or risk factor that is clinically significant and relevant.

Hyperuricemia should alert the clinician to an overall increased risk of Cardiovascular disease. Elevation of uric acid > 4 mg/dl should be considered a "Red Flag" in those patients at risk for cardiovascular diseases and should alert the clinician to strive and utilize a global risk reduction programme to reduce the complications of atherogenic process.[58]

Hayden and Tyagi et al have suggested the RAAS protocol for these patients to reduce the atherogenic process[58]

R – **R**eductase inhibitors (HMG Co-A)

A – **A**CE inhibitors, ARB

Aspirin

Adrenergic blockade

A - **A**ggressive control of diabetes

Aggressive control of B.P (losartan)[3]

Aggressive control of uric acid (allopurinol)

S – Life **S**tyle

Stop Smoking

DEFINITIONS USED IN PRESENT STUDY

1. DIABETES MELLITUS:

Criteria for the diagnosis of diabetes mellitus (modified form of American Diabetes Association, 2003)

1. Symptoms of diabetes + (R) blood glucose ≥ 200 mg/dl.
2. Fasting plasma glucose ≥ 126 mg/dl.
3. Two hour plasma glucose (Post prandial) ≥ 200mg/dl during an oral glucose tolerance test.

2. HYPERURICEMIA:

Hyperuricemia is defined as serum uric acid level ≥ 8mg/dl in males and ≥ 6 mg/dl in females.

3. BODY MASS INDEX:

It is estimated by using the formula : weight (kg)/ Height^2(m)

4. OBESITY:

Obesity is usually defined as body mass index > 30, body mass index between 25-30 kg/m^2 as overweight. Body mass index between 25-30 should be viewed as medically significant, especially in the presence of other risk factors like hypertension, diabetes.

Large scale epidemiological studies suggest that cardiovascular morbidity begins to rise when body mass index ≥ 25, suggesting that the cut of for obesity should be lowered.

WAIST HIP RATIO:

The waist is measured by taking a circumference that gives the narrowest measurement between the rib cage and the iliac crest. The hip measurement is taken by measuring at a level that gives the maximal measurement of hip over the buttocks. It is a simple, and convenient measurement that is unrelated to height, correlates closely with body mass index and waist hip ratio is an approximate index of intra abdominal fat mass and total body fat.

Waist hip ratio > 0.8 in women and > 1.0 in men being abnormal.

LIPID PROFILE ABNORMALITY

According to NCEP-ATP III guidelines, the following lipid values were considered as abnormal.

Triglycerides >150 mg/dl

HDL < 40 mg/dl (Male) and < 50 mg/dl (female).

MATERIALS AND METHODS

SETTING	:	Government Mohan Kumaramangalam Medical college, Salem-30.
COLLABORATIVE	:	Department of Biochemistry, Government Mohan Kumaramangalam Medical college, Salem-30.
STUDY DESIGN	:	Descriptive analytical study
PERIOD OF STUDY	:	February 2008 to September 2009
SAMPLE SIZE	:	70 Cases.
ETHICAL COMMITTEE APPROVAL	:	The present project was approved by the Ethical committee.

INCLUSION CRITERIA:

1. Patients with type 2 diabetes mellitus (patients were taken irrespective of their glycemic control and their duration of diabetes).
2. Patients who were above 40 years were included.
3. Both sexes were included.

EXCLUSION CRITERIA:

1. Patients with renal failure.
2. Pregnancy & lactating mothers.
3. Patients who were on long term diuretics & steroid.
4. Patients who were regularly consuming alcohol.
5. Patients who were on anti metabolite and chemotherapy drugs.
6. Patients who had hepatic & metabolic disorders.
7. Patients who had PVD/CVA/ Pulmonary Tuberculosis.
8. Renal transplant patients.

CONTROLS:

Subjects who were above 40 years and had normal blood sugar and who met the above exclusion criteria.

CONSENT:

The study group thus identified by the above criteria (inclusion and exclusion) were first instructed about the nature of study. Willing participants were taken up after getting a written informed consent from them.

MATERIALS:

Thus a total of 70 cases who satisfied the inclusion and exclusion criteria above were taken up for subsequent study. 30 age and sex matched subjects were kept as control.

CONFLICT OF INTEREST:

There was no conflict of interest.

FINANCIAL SUPPORT:

Nil.

LIMITATIONS:

1. Because of limited resources GTT, HbA_1C, leptin level, C peptide assay, plasma insulin assay could not be tested.

2. X ray chest was not performed is every case due to technical limitation.

3. Only serum uric acid levels were analysed. Urinary excretion and urate clearance was not done.

METHODS:

Selected socio- demographic, clinical, laboratory data were elicited from the patients and controls and recorded in proforma.

1. Socio demographic data.
    - Age
    - Sex
2. Clinical Data.
    - Body weight
    - Height
    - BMI, waist hip ratio (WHR)
    - Systolic / Diastolic blood pressure
    - Cardiovascular risk factors
    - Clinical examination

3. Laboratory Data:

- Blood urea estimation was done manually by using diacetyl monoxime method (DAM).
- Serum creatinine estimation was done by using COBAS auto analyser.
- Serum uric acid was done by using semi auto analyser.

PRINCIPLE:

Uric acid is converted by uricase to allantoin and hydrogen peroxide in the presence of peroxidase (POD) which oxidizes the chromogen to a red coloured compound which is read at 500mm.[65]

$$\text{Uric acid} + 2H_2O + O_2 \xrightarrow{\text{URICASE}} \text{Allantion} + CO_2 + H_2O_2$$

$$2H_2O_2 + 4\ \text{Aminopyrine} + \xrightarrow{\text{DHBS POD}} \text{Red quinolone} + H_2O + HCl$$

(DHBS 3,5 dicholoro-2 hydroxy benzene sulphonic acid)

STATISTICAL ANALYSIS:

Data was entered in Microsoft excel spread sheet and analysed statistically using standard statistical software. Student 't' values was applied for significance. Significance of 'P' value was below 0.05.

RESULTS

The total number of subjects included in this study was 100. Among those 100 subjects, 70 were cases (type 2 diabetes mellitus) and 30 were controls (non diabetic).

Table – 1 : Introduction

	CASES	CONTROLS
Total No.	70	30
Gender	M=43;F=27	M=18; F=12
Age (Years)	43 to 72	41 to 75
Mean age (Years)	59.13	56.97
BMI	19.6-29.4	18.4-26.0
WHR	0.73-1.14	0.76-1.12
FBS (mg/dl)	105-172	86-120
PPBS (mg/dl)	157-302	139-181
SUA (mg/dl)	2.8-8.3	2.9-5.3

ANALYSIS OF CASES AND CONTROL WITH RESPECT TO AGE:

The age of the subjects in the study group ranged from 43 to 72 years. The mean and standard deviation for age of the cases and controls were 59.13±9.11 and 56.97±8.41 respectively, there was no significant difference among the cases and controls with reference to the age. The distribution of cases and controls in relation to age is provided in table 2 given below.

Table 2 : Cases and Controls in relation to age

Age Group	Cases		Controls	
	No	%	No	%
40-50	14	20	6	20
51-60	21	30	10	33.33
61-70	26	37.14	11	36.66
71-80	9	12.85	3	10
Mean	59.13		56.97	
S.D.	9.11		8.41	

P = 0.0551 (Not Significant)

ANALYSIS OF CASES AND CONTROLS WITH RESPECT TO GENDER

Among 70 cases studied, there were 43 males and 27 females, among 30 controls there were 18 males and 12 females. The details are given in table 3 provided below.

Table 3 : Cases and Controls in relation to gender

Sex	Cases		Controls	
	No	%	No	%
Male	43	61.43	18	60
Female	27	38.57	12	40
Total	70	100	30	100

P = 0.7901 (Not significant)

The sex composition of the study group and control group does not differ.

ANALYSIS OF CASES AND CONTROL WITH RESPECT TO BMI:

Among 70 cases and 30 controls screened for BMI, none were obese. The mean and standard deviation for BMI of cases and controls were 24.93 ± 3.13 and 21.8 ± 2.3 respectively. The details are shown in Table 4 given below:

Table 4 : Cases and Controls in relation to BMI

BMI	Cases		Controls	
	No	%	No	%
< 25	34	48.57	24	80
≥ 25	36	51.42	6	20
Total	70	100	30	100
Mean	24.93		21.8	
S.D.	3.13		2.3	

P = 0.0002 (Significant)

The BMI of the study group was significantly higher than that of control group.

BLOOD SUGAR DISTRIBUTION AMONG CASES

The details of fasting and post prandial blood sugar distribution among the cases are shown in table 5 given below:

Table 5 : (F) BS and (PP) BS among cases

BL. Sugar	Mean	S.D.
F (BS)	132.79	36.72
PP (BS)	206.2	37.49

The mean and standard deviation for fasting blood sugar was 132.79±36.72 similarly for post prandial blood sugar was 206.02 ± 37.49 among diabetes. Thus showing their diabetic status was under the control.

DISTRIBUTION OF CASES AND CONTROLS IN RELATION TO SELECTED CARDIOVASCULAR RISK FACTORS

Analysis of cases and controls in relation to selected cardiovascular risk factors are provided in Table 6 given below.

Table 6 : Selected Cardiovascular Risk Factors

Risk Factor	Cases		Controls	
	No	%	No	%
Family History				
Yes*	20	28.57	7	23.34
No	50	71.43	23	76.66
* P value 0.5622 (Not Significant)				
Smoking among Males				
Yes**	19	27.14	8	26.66
No	51	72.85	22	73.33
** P value 0.5746 (Not Significant)				
Hypertension				
Yes***	18	25.71	7	23.33
No	52	74.27	23	76.67
*** P value 0.5044 (Not Significant)				

There was no significant difference between cases and controls in relation to selected cardiovascular risk factors.

DISTRIBUTION OF CASES AND CONTROLS IN RELATION TO SERUM URIC ACID LEVEL (SUA):

Serum uric acid in the study population and control varied from 2.8 to 8.3 and 2.9 to 5.3 mg/dl respectively. The mean and standard deviation of uric acid among cases was 5.25 ± 1.59 while in control it was 3.91 ± 0.98 respectively.

The details are shown in the table 7 given below.

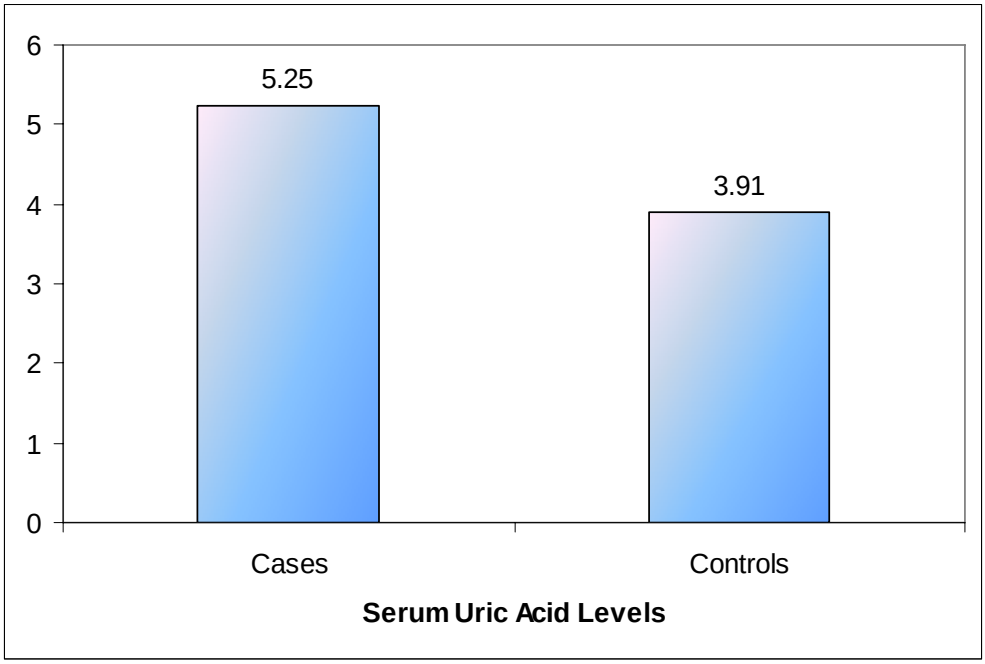
Table 7 : Serum Uric Acid level in diabetics and controls

Serum Uric Acid *	Cases		Controls	
	Mean	S.D.	Mean	S.D.
	5.25	1.59	3.91	0.98

* P value : 0.0001 (significant)

The serum uric acid level of diabetics was very much elevated compared with controls and it was highly significant.

Fig : 3 – Mean Serum Uric Acid levels in cases and controls



ANALYSIS OF HYPERURICEMIA IN CASES AND CONTROLS

Hyperuricemia is defined as SUA level ≥ 8 mg/dl in males and ≥6 mg/dl in females. 15 cases had hyperuricemia while none in controls. The results are displayed in table 8 given below:

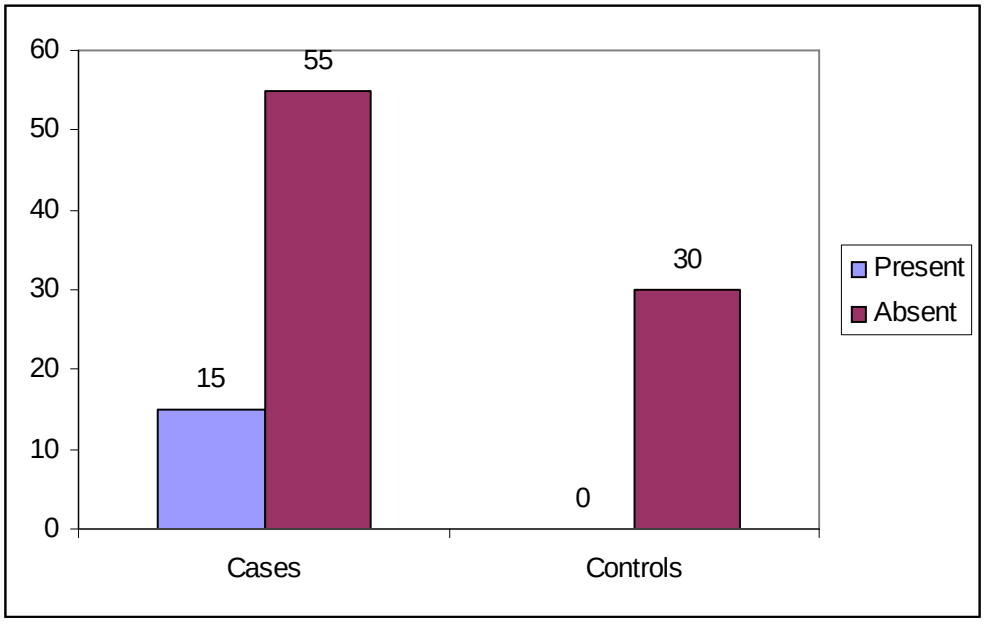
Table 8 : Hyperuricemia in Cases and Controls

Hyperuricemia	Cases				Controls			
	No	**%**	**Mean**	**S.D**	**No**	**%**	**Mean**	**S.D**
+	15	21.4	7.16	0.5	0	-	-	-
-	55	78.67	4.73	1.21	30	100%	3.91	0.98

*P = 0.0001 (Significant)

This table clearly shows that the prevalence of hyperuricemia is more in diabetic patients when compared to controls.

Fig. 4 : Hyperuricemia in Cases and Controls



ANALYSIS OF GENDER DISTRIBUTION WITH SERUM URIC ACID AMONG THE CASES

The mean value of serum uric acid was 5.06 ± 1.64 in males and 5.63 ± 1.12 in females and details are given in table 9 below.

Table 9 : Serum Uric Acid values in relation to gender among cases

Sex	No	Mean	S.D.	P Value
Male	43	5.06	1.64	0.0196
Female*	27	5.93	1.12	

*P Value = 0.0196 (Significant)

In the study group mean uric acid values were higher in females than males and the difference was statistically significant.

SERUM URIC ACID VALUE IN RELATION TO BMI IN CASES

The mean value of serum uric acid was 6.13 ± 1.45 in those with BMI > 25. It was significantly higher than compared to those having BMI < 25. The mean value of serum uric acid in BMI < 25 was 4.13±1.23.

The details are shown in table 10 given below:

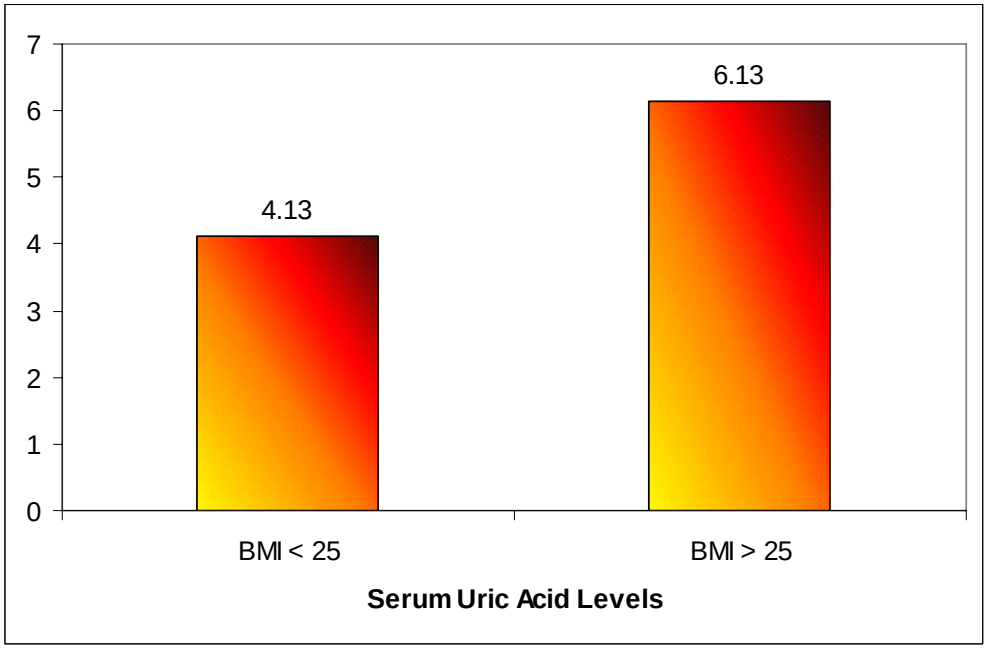
Table 10 : Uric Acid with regard to BMI among cases

BMI	No.	Mean	S.D.
< 25	34	4.13	1.23
> 25*	36	6.13	1.45

* P Value = 0.0001 (Significant)

Mean uric acid level was positively correlated with BMI.

Fig. 5 : SERUM URIC ACID VALUE IN RELATION TO BMI IN CASES



SERUM URIC ACID VALUE IN RELATION TO WAIST HIP RATIO (WHR)

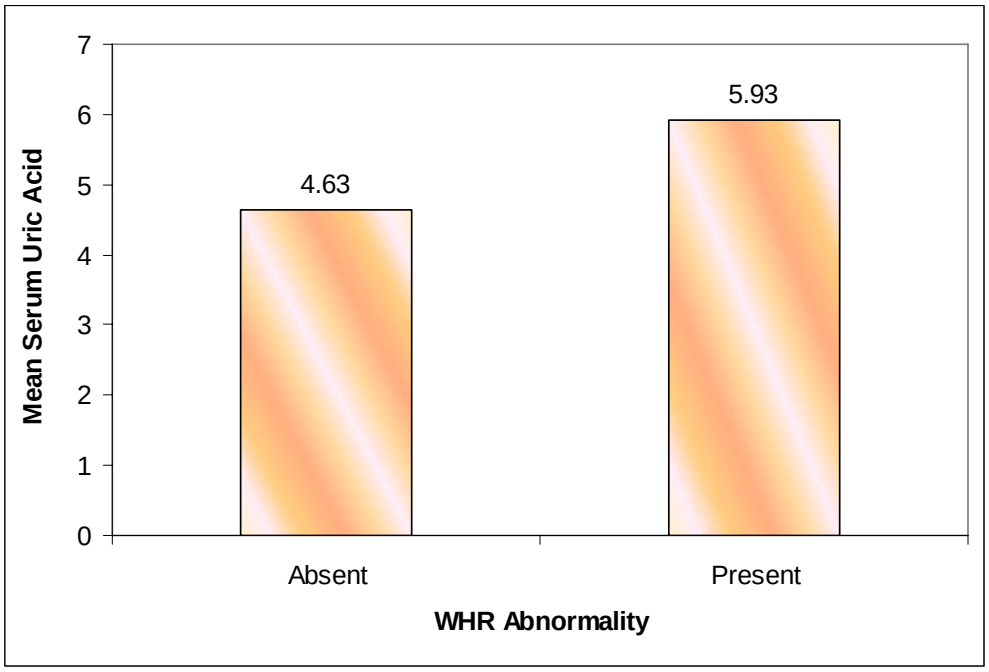
Uric acid level increases with increased WHR. The WHR abnormality was considered in 33 cases based on, WHR above 1.0 for men, above 0.8 for women and correlated with uric acid level was significant details are shown in table 11 given below:

Table 11 : Waist Hip Ratio and Hyperuricemia

WHR Abnormality	No.	Mean	S.D.
Yes*	33	5.93	1.37
No	37	4.63	1.3

* P Value = 0.0001 (Significant)

Fig 6 : Waist Hip Ratio and Hyperuricemia



SMOKING AND SERUM URIC ACID AMONG THE CASES (ONLY IN MALES)

The mean value of serum uric acid among smokers was 5.03±1.69 when compared to non smokers 5.32±1.42, but the difference was not significant statistically, this is shown in table 12 given below:

Table 12 : Uric Acid Values in relation to Smoking (only in males)

Smoking	No.	Mean	S.D.
Yes*	19	5.03	1.69
No	51	5.32	1.42

* P Value = 1.5472 (Not Significant)

SERUM URIC ACID VALUES IN HYPERTENSIVE PATIENTS

The mean serum uric acid level in the hypertensive group (6.45±1.15) was significant more than non hypertensive group (4.83±1.43) in the cases and the results are shown in the table 13 given below:

Table 13 : Serum Uric Acid values in relation to Hypertension

HT	No.	Mean	S.D.
Yes*	18	6.45	1.15
No	52	4.83	1.43

* P Value = 0.0001 (Significant)

SERUM URIC ACID LEVEL IN RELATION TO LIPID PROFILE ABNORMALITY

The mean serum uric acid level in patients with lipid profile abnormality was 6.67±0.94, while it was 4.75±1.44 in patients without lipid profile abnormality and it was highly significant. The results are shown in table 14 given below:

Table 14 : Serum Uric Acid value in relation to lipid profile abnormality

Lipid Profile Abnormality	No.	Mean	S.D.
Yes*	18	6.67	0.94
No	52	4.75	1.44

* P Value = 0.001 (Significant)

Table 15 : CAD and Hyperuricemia

Type of CAD	No. of Patients	Total no. of Hyperuricemia	Sex	%
Ischaemia	16	4	2M + 2F	25%
Infarction	8	4	1M + 3F	50%

This table was showing number of patients with Ischaemia – 16. Of these only 4 had hyperuricemia with equal sex distribution (1:1).

Number of patients with infarction was 8. Of these only 4 had hyperuricemia, one male and three female patients (1:3).

Percentage of hyperuricemia in infarction is higher than in ischaemia, and female patients were more involved in CAD than males in relation to hyperuricemia.

SERUM URIC ACID VALUE IN RELATION TO DURATION OF DIABETES

Mean value of Serum uric acid level was higher in longer duration (9-12 years) of diabetes 6.87±1.03, when compared to shorter duration (2-4 years) of diabetes 4.31±1.08. This is shown in table 16 given below:

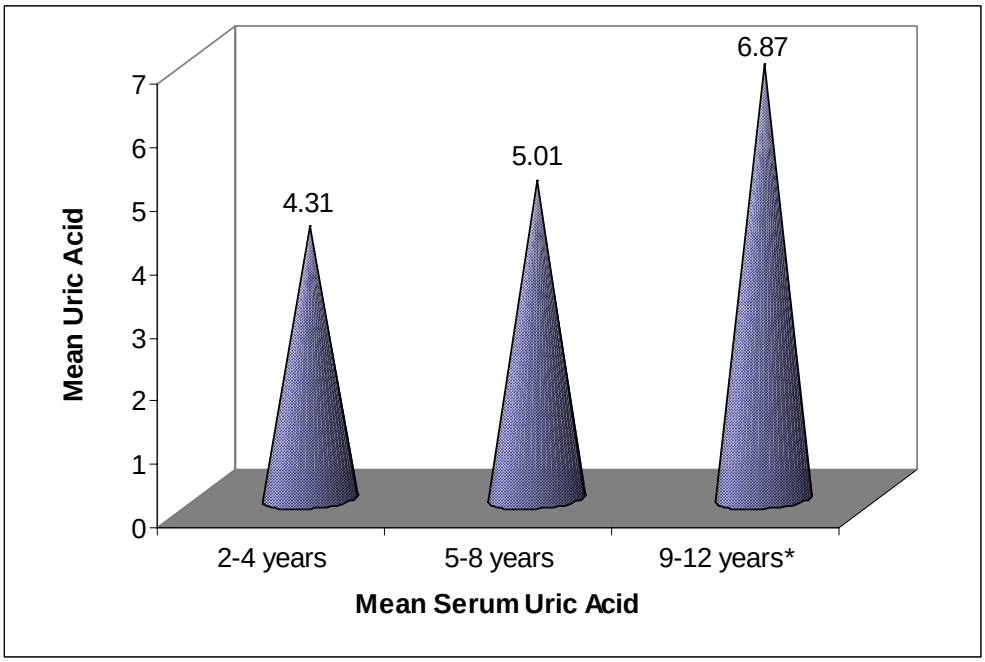
Table 16 : Duration of Diabetes and Hyperuricemia

DOD	No.	Mean	S.D.
2-4 years	12	4.31	1.08
5-8 years	37	5.01	1.891
9-12 years*	21	6.87	1.03

* P Value = 0.001 (Significant)

Uric acid level increases with increasing duration of diabetes and it was statistically significant.

Fig 7 : Duration of Diabetes and Hyperuricemia



DISCUSSION

Diabetes is the most common risk factor for cardiovascular disease, and it is present in nearly 25% adults and increases in prevalence with age.[2]

Hyperuricemia is one of the components of metabolic syndrome. “In the absence of gout the presence of hyperuricemia in patients with type 2 diabetes mellitus is an important marker as well as an added risk factor for atherosclerosis.”[7]

In this study the relation between serum uric acid level and diabetes was examined. Uric acid is a marker for CAD in combination with other risk factors among diabetics.

Though uric acid level and age was independent it is possible that duration of the illness may have an impact on uric acid levels.

In the present study females have higher uric acid level when compared to males. The mean uric acid value in males was 5.06±1.64

while in females it was 5.93±1.13, and the difference was statistically significant in this study. The possible reasons for such difference may be attributable to increased BMI and increased WHR among women.

In the present study serum uric acid correlated well with body mass index (BMI). The mean uric acid in those subjects with BMI > 25 was higher than those with BMI < 25 (6.13±1.45 Vs 4.13±1.23) and the difference was statistically significant.

Rathmann et al., assessed the various components of insulin resistance syndrome in young black and white adults. They concluded that body mass index showed strongest positive correlation with the uric acid among insulin resistant components.[62]

Waist hip ratio is an important measure of obesity, especially central obesity. Intrabdominal fat has significant implication for morbidity than subcutaneous fat present in buttocks and extremities.[40]

Abdominal obesity is a component of metabolic syndrome. Waist circumference > 102 cm in men and >88cm in women is

abnormal. In this study patient with higher waist hip ratio had higher uric acid level when compared with low waist hip ratio.

The mean uric acid value in patients with waist hip ratio abnormality and patients without waist hip ratio was 5.93±1.38 and 4.63±1.3 respectively and the difference was statistically significant.

Strong epidemiologic data have linked serum uric acid to hypertension in humans and experimental animal data suggests hyperuricemia causes hypertension.[63,64] The Olivetti heart study had shown a independent positive association between serum uric acid and development of hypertension.

When the level of serum uric acid in hypertensive patients was compared with non-hypertensive patients in cases, the difference was significantly higher in the present study.(6.45±1.15 vs 4.83±1.43)

Elevated triglycerides is the most important risk factor in acceleration of atherosclerosis. There is a significant relationship between serum uric acid and dyslipidemia. In the present study

dyslipidemia was noticed as a risk factor in those with CAD, who had significantly elevated serum uric acid levels. (6.67±0.94 vs 4.75±1.44)

"Uric acid stabilizes the platelet aggregation and enhances thrombotic tendency," thus suggesting hyperuricemia as a strong predictor of myocardial infarction and stroke.[66]

Patients with Poor metabolic control and longer duration of diabetes were more susceptible to develop various complications including hyperuricemia.[67] Our study also shows that higher level of serum uric acid was seen in patients with longer duration of diabetes when compared with shorter duration of diabetes, 6.87±1.03 (9-12yrs) vs 4.31±1.08 (2-4yrs) This difference was statistically significant.

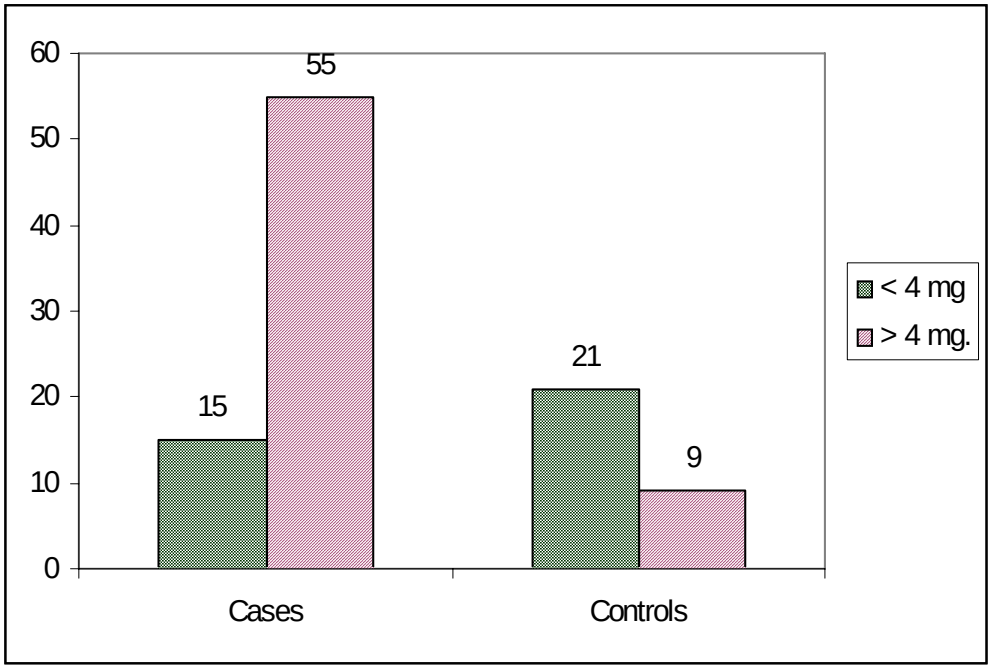
Uric acid >4 mg/dl should be considered as a "Red flag" in those patients at risk for cardiovascular disease.[58] In this study 78.57% of diabetic patients have serum uric acid level >4 mg/dl, while only 30% of the control have serum uric acid >4mg/dl. In these patients the clinician should strive to utilize global risk reduction programme to reduce the complications of atherogenic process. The details in relation to this study is shown in the table 17 given below:

Table 17 : Cases and Controls in relation to Uric acid

Serum Uric Acid	Cases		Controls	
	No	%	No	%
< 4 mg.	15	21.43	21	70
> 4mg.	55	78.57	9	30

P = 0.0001 (Significant)

Fig. 8 : Cases and Controls in relation to Uric acid



The association of serum uric acid with cardiovascular disease has been appreciated for nearly half a century. However, its role as a cardiovascular risk factor remains controversial.[68] In an epidemiologic follow up study an association between serum uric acid and cardiovascular disease was shown. The PIUMA study[69] also concluded that raised serum uric acid is a powerful risk marker for subsequent cardiovascular disease and all cause mortality.

Of the 70 cases of type 2 diabetes mellitus, hyperuricemia was observed in 15 patients which accounts for 21.43% of cases. Canon[70] showed a prevalence of hyperuricemia in 25% of longstanding uncontrolled diabetes. But in this study many of the cases were on treatment which might have affected the results.

A large body of evidence links uric acid with metabolic syndrome of insulin resistance, obesity, hypertension and dyslipidemia. In this study relationship between obesity, hypertension, dyslipidemia and hyperuricemia was statistically significant.

CONCLUSION

- Uric acid was significantly elevated in diabetic population.
- The serum uric acid level was independent of age and smoking status in males.
- Significant correlation was noticed between serum uric acid and BMI as well as WHR.
- Significant elevation of uric acid level was observed more among females.
- Elevated uric acid levels were significantly noticed among those with hypertension, dyslipidemia, coronary artery disease and chronicity of the diabetes.
- Uric acid level above 4 mg/dl in diabetic population (considered as a “Red flag” sign) was a marker or risk factor for CAD, which was present in 78% of study population.

SUMMARY

Diabetes mellitus is strongly associated with hyperuricemia. The role of uric acid as a independent risk factor for cardiovascular disease is a matter of controversy. The present study was proposed to assess the uric acid status in patients with diabetes mellitus and to find out its association with age, gender, BMI, WHR, smoking and CAD. With rigid criteria, patients were selected carefully and evaluated on social, clinical and laboratory aspects after getting institutional, ethical clearance and informed consent. 30 healthy age, sex matched individuals were kept as control. There were 43 males and 27 females in the study group and 18 males and 12 females in the control group. There was no significant difference among cases and controls in relation to age.

In study group, BMI below 25 was seen in 34 cases (48.57%), BMI above 25 seen in 36 cases (51.42%) which was significantly more than controls. BMI had significantly correlated with hyperuricemia. Similarly WHR was greater among women than men

in diabetics, which also correlated with elevated serum uric acid significantly.

Elevated serum uric acid level was noticed more among those who had hypertension dyslipidemia, coronary artery disease and they were significant. Patients with longer duration of diabetes also had elevated uric acid level.

The factors contributing to hyperuricemia in diabetes are,

1. Hyperinsulinemia acutely reduces urinary uric acid and sodium excretion.
2. Hyperinsulinemia imposes a chronic antinatriuretic and anti uricosuric effect on the kidney.
3. Microvascular disease in diabetes mellitus causes local tissue ischemia and decreased renal blood flow leading to ischemia with associated lactate production that blocks urate secretion in proximal tubules. Increased uric acid synthesis occurs due to increased purine metabolism, ischemia induced increased xanthine oxidase production, insulin resistance and diuretic use.

Routine annual estimation of uric acid among diabetics from the identification of diabetes will help the clinician to find out the changing trends of uric acid level which is likely to be influenced by control of blood sugar and development of hypertension, such cases should be carefully monitored for CAD as well as other vascular episodes.

Since uric acid is a confounding factor and multiple factors are involved for elevated uric acid. A meticulous control of blood sugar, hypertension, dyslipidemia among diabetics will bring down elevated uric acid level in diabetics.

Let us have a Moto of,

"Assess diabetics for risk factors;

Assist to control them and

Arrest the development of complications"

With the Pharmacological and non pharmacological means.

CASES MASTER CHART																		
S. No.	**Age (Yrs.)**	**Sex**	**DOD**	**BMI**	**WHR**	**Smoking**	**Family History of Diabetes**	**Systemic Hyper Tension**	**IHD**	**BS (F)**	**BS (PP)**	**Renal Parameters**	**USG Abd**	**ECHO / ECG**	**Lipid Profile Abnormality**	**Retino Pathy**	**Nauro pathy**	**Sr.Uric acid**
1	52	M	6	20.6	0.86	Y	N	N	N	136	222	N	N	N	N	N	N	4.2
2	69	M	10	27.8	1.08	Y	Y	Y	Y	122	203	N	N	MI	Y	Y	N	8.1
3	43	M	2	19.6	0.73	N	N	N	N	123	186	N	N	N	N	N	N	2.8
4	55	M	5	20.2	0.80	N	N	N	N	109	173	N	N	N	N	N	N	3.8
5	62	M	8	28.8	1.12	Y	N	N	N	137	233	N	N	N	N	N	N	3.0
6	51	M	3	21.9	0.86	N	Y	N	Y	119	173	N	N	MI	N	N	N	4.6
7	61	M	7	23.2	0.80	Y	N	N	N	149	200	N	N	N	N	N	N	3.5
8	47	M	3	20.4	0.78	N	Y	N	N	107	187	N	N	N	N	N	N	3.7
9	62	M	6	23.7	0.84	N	N	Y	Y	158	253	N	N	I	N	Y	N	4.8
10	44	M	4	23.3	0.83	N	N	N	N	172	192	N	N	N	N	N	N	4.0
11	71	F	12	27.7	0.91	N	N	Y	N	105	202	N	N	MI	Y	Y	Y	6.2
12	59	F	8	27.3	0.89	N	Y	N	Y	137	170	N	N	I	N	N	N	5.3
13	72	F	14	27.4	0.93	N	N	Y	Y	135	223	N	N	I	Y	Y	N	6.1
14	53	F	5	21.4	0.80	N	N	N	N	164	222	N	N	N	N	N	N	5.8
15	67	F	4	22.6	0.83	N	N	N	N	121	275	N	N	N	N	N	N	5.7

16	72	M	10	27.8	0.97	Y	N	Y	Y	153	192	N	N	I	Y	Y	N	6.4
17	60	F	8	28.1	0.94	N	N	N	Y	112	271	N	N	MI	N	N	N	7.9
18	47	F	5	20.2	0.80	N	N	N	N	117	175	N	N	N	N	N	N	5.8
19	55	F	7	24.8	0.84	N	Y	N	N	123	157	N	N	N	N	N	N	4.0
20	66	F	10	28.3	0.92	N	N	N	N	135	157	N	N	N	Y	Y	N	5.8
21	43	M	2	19.6	0.76	Y	N	N	N	139	192	N	N	N	N	N	N	3.8
22	67	M	7	20.4	0.80	Y	Y	N	Y	159	201	N	N	I	N	N	N	4.6
23	63	M	9	27.4	0.82	Y	N	N	Y	151	243	N	N	I	N	N	N	5.8
24	72	F	12	27.2	0.92	N	N	Y	N	119	231	N	N	N	Y	Y	N	6.3
25	59	M	10	27.4	1.14	Y	Y	Y	Y	147	243	N	N	I	N	N	N	8.1
26	57	F	6	28.2	0.81	N	N	Y	N	145	174	N	N	N	N	N	N	4.6
27	62	F	6	24.5	0.92	N	N	N	N	127	126	N	N	N	N	N	N	4.0
28	63	M	7	27.4	1.02	Y	Y	Y	Y	109	223	N	N	MI	N	N	N	6.5
29	60	F	10	27.3	1.12	N	Y	N	N	133	211	N	N	N	N	Y	N	6.1
30	58	F	9	28.4	1.10	N	N	N	Y	114	216	N	N	I	Y	N	N	5.7
31	61	M	7	22.3	0.80	Y	N	N	N	152	247	N	N	N	N	N	N	3.2
32	63	M	8	27.2	0.84	N	N	Y	N	120	196	N	N	N	N	N	N	4.6
33	69	M	10	27.4	1.02	N	Y	Y	Y	107	176	N	N	I	Y	Y	N	8.1
34	65	M	6	24.7	0.99	Y	N	N	N	112	181	N	N	N	N	N	N	5.6

35	53	M	7	22.3	0.84	N	N	N	N	141	243	N	N	N	N	N	N	5.0
36	54	M	6	23.0	0.86	N	N	N	N	143	251	N	N	N	N	N	N	4.8
37	67	F	12	28.6	1.08	N	Y	Y	Y	139	233	N	N	I	Y	Y	N	6.7
38	63	M	7	27.0	1.02	N	N	N	N	137	211	N	N	N	N	N	N	8.2
39	66	F	6	27.8	1.00	N	Y	N	N	111	209	N	N	N	N	N	N	5.4
40	61	M	6	23.8	0.88	N	N	N	N	142	231	N	N	N	N	N	N	3.0
41	62	M	6	20.8	0.80	Y	N	N	N	117	199	N	N	N	N	N	N	3.1
42	72	M	10	27.8	0.92	N	Y	Y	Y	121	201	N	N	I	Y	Y	Y	6.7
43	57	M	7	20.2	0.80	N	N	N	N	106	192	N	N	N	N	N	N	3.2
44	44	M	4	20.0	0.80	N	N	N	N	109	157	N	N	N	N	N	N	2.8
45	71	F	8	29.0	1.08	N	N	N	Y	151	245	N	N	MI	Y	N	Y	7.7
46	54	M	7	27.4	0.92	N	Y	N	N	149	211	N	N	N	N	N	N	5.2
47	63	M	7	27.8	0.88	N	N	N	N	108	238	N	N	N	Y	N	N	3.8
48	57	M	6	20.1	0.80	N	N	N	N	117	187	N	N	N	N	N	N	3.6
49	67	M	10	28.7	0.96	Y	N	N	Y	138	147	N	N	MI	N	N	N	6.6
50	69	M	12	27.8	1.00	N	N	Y	Y	161	191	N	N	I	Y	Y	N	6.6
51	59	M	9	21.3	0.78	N	N	N	N	152	301	N	N	N	N	N	N	4.6
52	72	M	10	27.6	0.92	N	Y	Y	N	145	203	N	N	N	Y	N	Y	6.6
53	48	M	3	23.2	0.82	Y	N	N	Y	157	219	N	N	I	N	N	N	4.2

54	57	F	7	26.8	0.88	N	N	N	N	144	200	N	N	N	Y	N	N	4.8
55	69	F	10	27.8	0.96	N	Y	N	Y	133	231	N	N	I	N	Y	N	2.9
56	52	F	5	27.0	0.90	N	N	N	N	138	203	N	N	N	N	N	N	4.2
57	48	F	6	21.2	0.80	N	N	Y	N	146	180	N	N	N	N	N	N	8.0
58	47	M	5	20.6	0.78	Y	N	N	N	142	302	N	N	N	N	N	N	3.1
59	62	M	7	27.4	1.07	N	N	N	Y	150	251	N	N	I	N	N	N	6.3
60	55	M	3	23.2	0.92	Y	N	N	N	109	178	N	N	N	N	N	N	4.7
61	65	M	8	27.8	1.02	N	Y	N	N	115	203	N	N	N	N	Y	N	6.0
62	63	F	7	29.4	0.80	N	N	N	Y	126	241	N	N	I	N	N	N	4.2
63	72	F	14	29.0	1.09	N	Y	Y	N	152	199	N	N	N	Y	Y	Y	6.1
64	51	F	3	23.1	0.84	N	N	N	N	132	173	N	N	N	N	N	N	6.4
65	50	F	6	21.4	0.87	N	N	N	N	106	161	N	N	N	N	N	Y	5.5
66	44	M	3	19.6	0.78	Y	N	N	N	119	172	N	N	N	N	N	N	2.8
67	49	F	3	20.1	0.81	N	N	N	N	137	253	N	N	N	N	N	N	5.9
68	72	M	12	28.4	1.09	Y	Y	N	N	139	171	N	N	N	Y	Y	Y	8.3
69	45	F	7	24.7	1.06	N	N	N	N	151	189	N	N	N	N	N	N	4.9
70	49	M	12	29.0	1.08	N	Y	Y	Y	140	177	N	N	MI	N	Y	N	5.9

CONTROLS MASTER CHART																		
S. No.	**Age (Yrs.)**	**Sex**	**DOD**	**BMI**	**WHR**	**Smoking**	**Family History of Diabetes**	**Systemic Hyper Tension**	**IHD**	**BS (F)**	**BS (PP)**	**Renal Parameters**	**USG Abd**	**ECHO / ECG**	**Lipid Profile Abnormality**	**Retino Pathy**	**Nauro pathy**	**Sr.Uric acid**
1	54	M	6	20.6	0.83	Y	Y	N	N	92	154	N	N	N	N	N	N	3.7
2	46	M	3	19.4	0.80	N	N	N	N	78	142	N	N	N	N	N	N	5.2
3	61	M	8	20.3	0.81	N	Y	N	N	106	148	N	N	N	N	N	N	2.9
4	64	M	10	25.4	0.84	N	N	Y	N	110	147	N	N	N	N	N	N	3.6
5	41	F	2	18.6	0.78	N	N	N	N	110	167	N	N	N	N	N	N	3.6
6	59	F	7	21.4	0.82	N	N	N	N	120	172	N	N	N	N	N	N	4.5
7	67	M	8	22.4	1.10	Y	Y	Y	N	112	161	N	N	N	N	N	N	5.5
8	52	M	3	20.6	0.81	Y	N	N	N	118	147	N	N	N	N	N	N	3.2
9	63	M	8	24.7	0.88	N	N	N	N	120	162	N	N	N	N	N	N	3.7
10	60	F	4	23.8	0.87	N	N	N	N	116	139	N	N	N	N	N	N	3.8
11	55	F	3	25.7	0.80	N	N	Y	N	86	168	N	N	N	N	N	N	4.3
12	49	F	3	19.6	0.78	N	N	N	N	92	167	N	N	N	N	N	N	5.2
13	44	M	3	18.4	0.82	Y	N	N	N	118	149	N	N	N	N	N	N	3.8
14	55	M	6	20.4	0.83	N	N	N	N	112	160	N	N	N	N	N	N	3.2

15	57	M	7	21.2	0.84	Y	N	N	N	113	163	N	N	N	N	N	N	4.9
16	62	M	5	26.0	1.02	N	Y	N	N	116	172	N	N	N	N	N	N	1.3
17	67	F	7	25.3	0.90	N	N	Y	N	106	180	N	N	N	N	N	N	3.9
18	49	F	23	20.6	0.84	N	N	N	N	112	142	N	N	N	N	N	N	3
19	51	F	3	21.4	0.86	N	N	N	N	119	167	N	N	N	N	N	N	3.7
20	55	M	3	20.8	0.80	N	Y	Y	N	106	143	N	N	N	N	N	N	4
21	66	F	10	25.8	0.87	N	N	N	N	111	168	N	N	N	N	N	N	3.4
22	62	M	9	23.2	0.83	N	N	N	N	107	167	N	N	N	N	N	N	3.6
23	64	M	8	25.6	0.82	Y	Y	N	N	120	148	N	N	N	N	N	N	3.8
24	47	M	2	20.0	0.84	N	Y	N	N	110	151	N	N	N	N	N	N	3.7
25	53	F	6	19.6	0.76	N	N	N	N	105	170	N	N	N	N	N	N	3.3
26	64	F	5	20.3	0.80	N	N	N	N	96	164	N	N	N	N	N	N	3.1
27	73	M	2	20.4	0.81	Y	N	Y	N	98	170	N	N	N	N	N	N	5.2
28	74	M	2	19.6	0.80	N	N	N	N	102	181	N	N	N	N	N	N	5.1
29	63	F	7	18.4	0.80	N	N	N	N	100	176	N	N	N	N	N	N	3.1
30	75	M	8	25.6	1.08	Y	N	Y	N	120	170	N	N	N	N	N	N	3.4